Guideline Series 84: **MUTAGENICITY**

EPA Reviewer: Irving Mauer, PH.D. Date: 11/09/94
Immediate Office, Toxicology Branch-I(7509C)
EPA Branch Chief: Karl P. Baetcke, PH.D. Date: 2/8/95
Toxicology Branch-I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Other Genotoxicity: Unscheduled DNA Synthesis (UDS) in Hepatocytes (HPC) from Treated Rats (in vivo/in vitro DNA repair test)

TOX. CHEM. NO.: 253

P.C.CODE: 024002

MRID NUMBER: 429623-03

TEST MATERIAL: Copper 8-Quinolinolate

SYNONYMS: RO 17-0099/000 (oxine copper); copper oxinate

STUDY NUMBER(S): B-154'904

SPONSOR: (042567) La Quinoleine SA, via International Regulatory Consulting, Washington, DC

TESTING FACILITY: F. Hoffmann-La Roche, Basel (Switzerland)

TITLE OF REPORT: In Vivo/In Vitro Rat Hepatocyte DNA Repair Test With the Fungicide RO 17-0099/000 (Oxine Copper-Copper 8-Quinolinolate) (Unscheduled DNA Test).

AUTHOR(S): S. Strobel

REPORT ISSUED: September 12, 1990

CONCLUSION(S) - Executive Summary: Reported as negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures isolated from male rats treated orally up to 3000 mg/kg, as determined by radioactive tracer procedures [nuclear silver grain counts].

Classification: UNACCEPTABLE

This study does not satisfy the requirement for FIFRA Test Guideline 84-2 for other genotoxic mutagenicity data, for the reasons stated in REVIEWER'S DISCUSSION.

[NAME OF TECHNICAL] **UNSCHEDULED DNA SYNTHESIS**

A. MATERIALS

1. Test Material: Ro 17-0099/000
   Description: Olive-green powder
   Lot/Batch #: 211 188
   Purity: 99.7% a.i.
   Stability of compound: Stable
   CAS #: 10380-28-6
   Structure: bis (8-quinolinolato) copper ($C_{18}H_{12}CuN_2O_2$]
   Solvent used: SSV: 0.5% sodium carboxymethylcellulose, 0.5% benzyl-ethanol, 0.4% Tween 80 in 0.9% [aqueous] sodium chloride.

2. Control Materials:
   Solvent/final concentration: SSV, 10 ml/kg
   Positive (concentrations, solvent): Dimethylnitrosamine, 15 mg/kg, in 0.9% sodium chloride.

3. Test compound concentrations used: Male rats (1-3 per dose group) were gavaged once at six dose levels (100-3000 mg/kg), and sacrificed 4 or 16 hours later.

4. Test Cells/Performance: Primary rat hepatocytes were isolated by in situ collagenase perfusion, established on cover slips, exposed to tritiated thymidine for 18 hours, and prepared for autoradiography by standard (published) procedures. After six days in the dark at 4^0C, cells were stained, and the number of nuclear silver grains counted in 25 cells per/coverslip (200 cells per animal), and normalized to the SSV vehicle control (providing evidence of unscheduled DNA synthesis, UDS).

   Evaluation Criteria: Significant increase in net nuclear counts over control, plus proportion of cells in repair.

C. REPORTED RESULTS: In the first of two trials, no induction of UDS was evident at either the 4 hours or 16 hours sampling times in hepatocyte cultures from rats treated up to 3000 mg/kg. In the second experiment, dose levels of 1500 mg/kg and more were hepatotoxic; no increased UDS was found at doses that could be evaluated (HDT = 1250 mg/kg)

D. REVIEWER'S DISCUSSION/CONCLUSIONS: The assay appears to have been performed without any major deficiencies, and in a manner such as to generate valid results. However:

(1) No explanation is provided why only males were treated, considering the acknowledged possible confounding factors listed on page 16 of the Final Report (last paragraph), to wit: "There might be several factors influencing the results in this test system, eg, variability between the animals, seasonal variations concerning physiological conditions. Furthermore mixed cell populations as primary hepatocytes have certain instabilities. The decision whether a compound is called DNA repair-inducing or not therefore relies exclusively on biological relevance."

(2) Insufficient documentation of the "slight hepatotoxicity" of test article at the HDT.

E. Was test performed under GLPs (is a quality assurance statement present)? Yes.

F. Appendix attached: Yes, Data Tables.

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